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# Serotonin Transporter Imaging in Multiple System Atrophy and Parkinson Disease

Running title: *[$^{11}$C]DASB in MSA and PD*

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**Abstract**

Background: Both Parkinson disease (PD) and Multiple System Atrophy (MSA) exhibit degeneration of brainstem serotoninergic nuclei, affecting multiple subcortical and cortical serotoninergic projections. In MSA, medullary serotoninergic neuron pathology is well documented, but serotonin system changes throughout the rest of the brain are less well characterized.

Objectives: To use serotonin transporter [$^{11}$C]3-amino-4-(2-dimethylaminomethyl-phenylsulfaryl)-benzonitrile Positron Emission Tomography (PET) to compare serotoninergic innervation in subjects with MSA and PD.

Methods: We performed serotonin transporter PET imaging in 18 MSA, 23 PD, and 16 normal control subjects to explore differences in brainstem, subcortical, and cortical, regions of interest.

Results: MSA subjects showed lower serotonin transporter distribution volume ratios compared to PD subjects in the medulla, raphe pontis, ventral striatum, limbic cortex and thalamic regions but no differences in dorsal striatal, ventral anterior cingulate, or total cortical regions. Control subjects showed greater cortical serotonin transporter binding compared to PD or MSA groups but lower serotonin transporter binding in the striatum and other relevant basal ganglia regions. There were no regional differences in binding between MSA-P (n=8) and MSA-C (n=10) subjects. Serotonin transporter distribution volume ratios in multiple different regions of interest showed an inverse correlation with severity of Movement Disorders Society Unified Parkinson's disease Rating Scale (MDS-UPDRS) motor score in MSA subjects but not PD subjects.

Conclusions: Brainstem and some forebrain subcortical region serotoninergic deficits are more severe in MSA compared to PD and show an MSA-specific correlation with the severity of motor impairments.

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## Introduction

Dysfunction of caudal brainstem serotoninergic raphe nuclei is suggested to occur early in Parkinson disease (PD)[1]. The relative frailty of these nuclei in PD may relate to their high baseline metabolic activity[2] or their key role in interconnected brainstem projection system networks[3] implicated in the cell-to-cell spread of misfolded synuclein. Multiple System Atrophy (MSA) is a parkinsonian disorder with neuronal cell loss in several neurotransmitter projection systems[4]. There are 2 clinical subtypes of MSA, a parkinsonian subtype (MSA-P), presenting primarily with parkinsonism, and a cerebellar subtype (MSA-C) presenting as a progressive cerebellar disorder with later expression of parkinsonism. MSA is characterized by glial cytoplasmic synuclein pathology rather than the neuron inclusions characteristic of PD[5]. There is clear neuropathologic evidence of serotoninergic neuronal loss in the caudal brainstem raphe nucleus complex in MSA[6, 7]. These neurons are known to project within the caudal brainstem and to motor and intermediolateral areas of the spinal cord. Their degeneration may contribute to MSA-specific features, including respiratory and autonomic dysfunction.

We know less about the extent of rostral serotoninergic projection system degeneration in MSA compared to PD. Rostral serotoninergic projections to the striatum, thalamus, and limbic cortices are implicated in PD as risk factors for sleep difficulties[8], affective symptoms[9], and weight changes[10]. Similar non-motor features are common and severe in MSA[11] although their biological basis is less well understood. [$^{11}$C]3-amino-4-(2-dimethylaminomethyl-phenylsulfaryl)-benzonitrile (DASB) is a positron emission tomography (PET) tracer that binds to the serotonin transporter (SERT) and can quantify regional serotoninergic projection terminal density[12-14], providing an opportunity to examine rostral serotoninergic projection system terminal integrity in patients with MSA compared to PD.

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**Methods**

We conducted a single-center, observational, cross-sectional neuroimaging study to evaluate rostral brain [$^{11}$C]DASB binding in MSA and compared these findings to existing DASB PD participant data available at the University of Michigan (UM) PET center. Subjects were recruited from Movement Disorders Clinics and through a web-based posting on a UM human subjects recruitment website (https://umhealthresearch.org/). All subjects signed informed consent documents approved by the UM Medical Institutional Review Board (IRBMED).

MSA subjects were 30-80 years old with a diagnosis of Possible or Probable MSA of the parkinsonian subtype (MSA-P) or cerebellar subtype (MSA-C) according to the MSA Second Consensus Criteria[15] and had a Mini-Mental State Examination (MMSE) score of 24 or greater. PD subjects were 45 years of age or older with modified Hoehn and Yahr stages 1-4 and met UK Brain Bank Clinical Diagnostic Criteria for PD[16]. PET data on the PD subjects in this cohort has been reported previously[17]. We excluded subjects with contraindications to MRI or PET imaging and those taking serotoninergic or anticholinergic medications in the 2 months preceding enrollment. For comparison to both PD and MSA, we included DASB data obtained from our PET center on a group of normal control subjects.

All subjects underwent [$^{11}$C]DASB PET imaging. Methods for our group's [$^{11}$C]DASB approach are detailed elsewhere[17, 18]. Briefly, we injected subjects with an intravenous bolus followed by an 80-minute infusion of [$^{11}$C]DASB. PET images were motion-corrected and normalized into a common atlas space using NeuroStat software (https://neurostat.neuro.utah.edu). We defined volumes of interest (VOI), including Brodmann areas and subcortical gray matter structures, on PET images using a Talairach brain atlas[19].

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These brain regions were identified on normalized parametric $K_1$ PET images using a set of predefined Talairach atlas regions through the NeuroStat software package (additional details on this approach are described elsewhere[20, 21]). We used equilibrium modeling to estimate the distribution volume in each voxel. Distribution volume ratios (DVRs) were calculated as a mean for each set of paired right and left hemisphere VOIs. We similarly calculated the mean of right and left brainstem VOIs including the medulla, raphe pontis, dorsal raphe, substantia nigra. Given the potential for the confounding influence of partial volume effects in the cerebellum in an MSA cohort, a disorder characterized by regional cerebellar atrophy, we used superior supratentorial white matter as a normalization reference region for calculating individual subjects' [$^{11}$C]DASB DVR. We selected this region because it had a relatively lower level of [$^{11}$C]DASB binding, not differing significantly between PD and MSA subjects. Another PET imaging group used a similar approach and reported low reference region SERT binding[22].

We explored differences in intergroup DVRs in several different VOIs. The medulla, raphe pontis, dorsal raphe, substantia nigra, ventral striatum, ventral anterior cingulate cortex (Brodmann Area 24) and thalamus were defined on atlas images. Distinct from the ventral striatum, we defined the dorsal striatum VOI as the voxel-adjusted mean of the bilateral caudate nucleus and putamen. Limbic cortex was defined using the amygdala, hippocampus, and insula VOIs. The total cerebral cortex was defined using voxel adjusted volumes specific to relevant Brodmann areas and limbic regions identified on the NeuroStat atlas and the thalamic VOI was identified through the Talairach atlas. We used descriptive statistics to display means and proportions between MSA, PD and NC groups. We used two sample t-tests to compare MSA and PD subjects in each of these VOIs. We conducted exploratory analyses within PD and MSA groups to evaluate for bivariate correlations (Pearson's r) between regional DASB DVR and

clinical scales including the Movement Disorders Society revised Unified Parkinson's disease Rating Scale (MDS-UPDRS) motor examination, the Montreal Cognitive Assessment (MoCA), the Geriatric Depression Scale (GDS), and the Epworth Sleepiness scale (ESS).

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**Results**

59 total subjects consented to participate in the study, but we excluded 2 subjects from analysis (1 MSA subject who could not complete the [$^{11}$C]DASB scan; 1 MSA subject due to taking a serotonergic medication), leaving a total cohort of 57 (23 PD, 18 MSA, 16 NC). Within the MSA group, there were 10 MSA-C subjects and 8 MSA-P subjects. We found no intergroup differences in any of the regions of interest on [$^{11}$C]DASB PET imaging between the two MSA subtypes, so they were subsequently combined into one group for comparison with PD (**Table 1**).

**Table 1** shows the differences between the groups in mean [$^{11}$C]DASB DVRs in the selected ROIs. As expected, DASB binding in the cortical VOIs was higher in the NC group compared to PD or MSA subjects. Interestingly, NC subjects showed a lower range of DASB binding in the striatum, ventral striatum, substantia nigra, dorsal raphe, and raphe pontis. There were no significant differences between PD and MSA subjects in total cortical, striatal, or substantia nigra [$^{11}$C]DASB DVRs. MSA subjects showed significantly lower [$^{11}$C]DASB DVRs in the thalamus, limbic cortex, ventral striatum, raphe pontis, and medulla compared to PD subjects. **Figure 1** depicts the DASB binding overlap between MSA and PD subjects in many supratentorial regions with qualitatively lower DASB binding in MSA in the limbic cortex and

caudal brainstem. There were no sex differences seen within the PD group or within the MSA group in DASB DVR in any of the ROIs.

MSA and PD subjects did not differ in MDS-UPDRS motor exam, MoCA, GDS, or ESS scores (Table 1). Correlation between these clinical variables and regional DASB DVR are presented in Supplementary Tables 1 and 2. Given the potential for inflated type 1 error due to multiple comparisons, these bivariate correlations are intended to be interpreted as hypothesis generating in nature. For the most part, MoCA, GDS, and ESS scores did not show a consistent correlative pattern with DASB DVR in either PD or MSA subjects. Interesting MSA subjects showed an inverse correlation between elevated MDS-UPDRS scores and lower DASB DVR seen in multiple different brain regions (Supplementary Figure 1). Outside of the striatum, these associations were not seen in PD subjects. Clinical data was available for only 4 of the 8 total MSA-P subjects, limiting our ability to conduct MSA subtype-specific analyses. Even so, among the 10 MSA-C subjects with available clinical data, similar patterns of inverse correlations were seen between MDS-UPDRS motor score and DASB DVR including in the total cortex ($r=-0.7140$, $p=0.0204$), striatum ($r=-0.7054$, $p=0.0227$), ventral striatum ($r=-0.7457$, $p=0.0133$), and ventral anterior cingulate ($r=-0.7930$, $p=0.0062$), but not in any of the other regions of interest.

**Discussion**

Relative to PD participants, MSA participants showed comparable levels of DASB binding in neocortical and dorsal striatal regions of interest but lower [$^{11}$C]DASB DVRs in key subcortical regions including the thalamus, ventral striatum, and limbic cortex as well as greater reductions in caudal brainstem DASB binding in the raphe pontis and medulla. MSA and PD

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subjects showed lower cortical DASB binding compared to NCs but higher striatal, midbrain, and pontine DASB binding. These MSA/PD region-specific findings may reflect the presence of compensatory physiology in subcortical serotoninergic systems. Lower DASB binding in MSA subjects in various brain regions correlated with greater motor impairment on the MDS-UPDRS motor exam. Our findings are from a relatively small cohort and may very well be impacted by multiple comparisons. For this important reason, they require replication in independent datasets. Nevertheless, these data comprise the first [$^{11}$C]DASB study in MSA. Our findings confirm the presence of lower brainstem serotoninergic pathology in MSA and raise the possibility of relatively selective rostral serotoninergic network abnormalities as a distinctive pathological feature of MSA.

The rostral serotoninergic raphe complex, located in the midbrain/rostral pons, gives rise to 2 distinct groups of ascending fibers—the dorsal and ventral/median raphe pathways. The dorsal raphe projects to the striatum and globus pallidus, while the ventral/median raphe sends projections to other forebrain regions, including the thalamus, hypothalamus, and limbic structures. Previous neuropathological studies demonstrated advanced serotoninergic neurodegeneration in the medullary raphe complex of MSA patients[6, 7, 23], a result consistent with our DASB PET findings. In contrast to the marked caudal brainstem serotoninergic neuron loss, a separate postmortem study showed only mild degeneration of the midbrain dorsal and median raphe complex in MSA, comprising an intermediate stage between normal control subjects and more severe findings found in Lewy body dementia (LBD) subjects[24]. In this latter postmortem study, the MSA subjects had a mean disease duration of 7 years. Our study expands on these findings by characterizing serotoninergic system changes in MSA participants with an average disease duration of only 3 years. The *in vivo* SERT density measurements of the cortex and

dorsal striatum in our MSA subjects was similar to PD and consistent with prior postmortem findings. Our finding of comparable *in vivo* serotonin transporter density in the cortex and dorsal striatum in MSA and PD subjects could support the conclusion that abnormalities of some key serotoninergic projections are similar in PD and MSA. We found significant differences in some regions, suggesting differential loss of serotoninergic terminals and perikarya. Alternatively, SERT expression might be differentially regulated in PD and MSA, possibly reflecting differential compensatory capacity of serotoninergic systems in these 2 disorders. Longitudinal studies using multiple serotoninergic tracers are needed to clarify what PET findings reflect degenerative terminal loss versus endogenous compensatory responses.

Interestingly, MSA and PD subjects showed lower cortical but higher basal ganglia, midbrain, and pontine DASB DVRs compared to controls. There are several possible explanations for these intergroup findings including the possibility that the serotoninergic system may show unique compensatory features in synucleinopathies. Prange et al recently reported increased DASB binding in the ventral striatum and anterior cingulate cortex of PD patients with apathy, suggesting that regional DASB elevations may occur in the setting of local neurodegeneration[25]. Another possibility is that rising SERT density is not simply a synaptic phenomenon but might also carry an autoregulatory role in the proximal cell bodies of serotoninergic projection neurons. A electrophysiologic study has shown that local application of SSRIs to the dorsal raphe nucleus of mice leads to local SERT inhibition at the level of the cell bodies and subsequent enhancement of synaptic serotonin release[26]. A third possibility is that our use of the superior supratentorial white matter as a reference region may have affected intergroup comparisons. This approach has not been reported or studied previously for DASB. We chose this region rather than the cerebellar DASB reference region given the potential for cerebellar

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pathology in MSA to bias intergroup comparisons. It is worth noting however, that supratentorial white matter pathology has been described in MSA compared to controls[27]. As such, this region may not be free of bias. Prospective validation of this approach against a model dependent on arterial sampling will be needed moving forward.

These results showing elevated regional DASB binding in PD compared to controls in the rostral brainstem and basal ganglia contrast with those reported in other cohorts[8, 28]. At least one PD study suggests that certain subcortical regions may show declines in DASB binding with advancing disease duration[29]. Nevertheless, the story of how regional DASB binding changes in PD is more nuanced and does not fit a monotonic, unidirectional pattern. Paradoxical elevations in DASB binding in the hypothalamus and hippocampus compared to controls have been reported in PD[30], as have paradoxical PD DASB upregulations in subjects with depression in the amygdala, hypothalamus, caudal raphe nuclei, and posterior cingulate cortex[31]. Differences in published DASB PD findings most likely reflect the complicated influence of baseline differences in serotoninergic integrity and genetic risk factors, variability across cohorts in disease duration, previous use of drugs relevant to the serotoninergic nervous system, and heterogeneity of clinical features known to correlate with serotoninergic pathology. A multicenter, PD observational study involving multiple serotoninergic tracers would be the optimal next step to better understanding the natural history of DASB bindings in synucleinopathies.

Our exploratory clinical correlative analyses showed an MSA-specific inverse correlation between severity of motor impairment and serotoninergic integrity in several different cortical, basal ganglia, and brainstem regions of interest. This is a novel finding and suggests that serotoninergic degeneration may be a possible therapeutic target for motor progression in MSA.

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Our findings are potentially confounded by the possibility of type-1 error and should be interpreted cautiously.

In addition to its cross-sectional design, another relevant limitation of our study is its lack of a uniform clinical assessment battery; the MSA and PD subjects were recruited and imaged through different clinical research protocols. MSA and PD are known to have overlapping clinical features, but distinctive disease-specific clinical factors possibly related to the serotoninergic system dysfunctions. We were also missing clinical data in 4 MSA-P subjects. PD subjects were on average 6.6 years older than MSA subjects and had mean disease duration that was 2 years longer. These findings may very well have impacted the results of our study. For example, it is possible that the clinical correlations seen between MDS-UPDRS scores and DASB DVRs in MSA subjects only reflect dynamic changes seen in early disease that reach a ceiling effect as disease duration advances. The higher overall MDS-UPDRS scores seen in MSA subjects in our cohort though would argue slightly against the possibility that MSA subjects in our cohort may have less advanced parkinsonism compared to PD subjects.

The potential of the ascending serotoninergic projection system as a biomarker or therapeutic target in MSA is yet to be determined. Nevertheless, given the paucity of current MSA treatments and the clinical availability of serotoninergic drugs targeting different 5HT receptor classes, understanding serotoninergic system alterations in MSA and other synucleinopathies may have diagnostic and therapeutic relevance. The present study is a step towards elucidating serotoninergic network dysfunction in this rare and complex disease.

**Author Roles**

**KLC:** writing, editing of the final version of the manuscript.

**PD:** design, execution, analysis, editing of the final version of the manuscript

**RAK:** design, execution, editing of the final version of the manuscript

**SG:** design, execution, editing of the final version of the manuscript

**CCS:** editing of the final version of the manuscript

**RLA:** writing, editing of the final version of the manuscript

**VK:** analysis, writing, editing of the final version of the manuscript

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**Table 1:** Cohort Characteristics and regional [$^{11}$C]DASB distribution volume ratios (DVR)

| | Parkinson disease (PD; n=23) | Multiple System Atrophy (MSA; n=18) | Normal Controls (n=16) | Chi-square/t-test p-value comparing PD to MSA |
|---|---|---|---|---|
| Age (years) | 66.2 (6.7) | 59.6 (7.6) | 66.0 (5.2) | t=2.932 p=0.006 |
| Sex | F=6, M=17 | F=8, M=9 | F=10, M=6 | Chi-square=1.89 p=0.17 |
| Disease Duration (years) | 4.9 (4.1) [range 1-12 years] | 2.9 (2.8) [range 1-11 years] | -- | t=1.713 p=0.095 |
| Modified Hoehn and Yahr (HY) Scale | HY1 (n=2); HY1.5 (n=4), HY2 (n=9), HY2.5 (n=6), HY3 (n=2) | -- | -- | |
| MDS-UPDRS Motor exam score | 25.522 (9.050) | 30.25 (19.033) [n=14] | -- | t= 1.023 p=0.314 |
| Montreal Cognitive Assessment Score | 25.565 (2.352) | 24.333 ( 4.451) [n=15] | -- | t=1.115 p=0.272 |
| Geriatric Depression Scale Score | 7.217 (4.512) | 8.857 (4.504) [n=14] | -- | t= 1.073 p=0.291 |
| Epworth Sleepiness Scale Score | 6.826 (4.141) | 6.571 ( 3.877) [n=14] | -- | t=0.186 p=0.854 |
| Region of Interest | | | | |
| Total Cortex | 1.267 (0.130) | 1.232 (0.093) | 1.792 (0.136) | t=0.964 p=0.341 |
| Caudate & Putamen | 2.232 (0.182) | 2.210 (0.192) | 2.007 (0.175) | t=0.379 p=0.707 |
| Thalamus | 2.381 (0.209) | 2.187 (0.164) | 2.103 (0.236) | t=3.243 p=0.002 |
| Limbic Cortex | 1.553 (0.130) | 1.454 (0.138) | 1.799 (0.144) | t=2.365 p=0.023 |
| Ventral Striatum | 2.388 (0.194) | 2.205 (0.241) | 1.959 (0.178) | t=2.702 p=0.010 |
| Ventral Anterior Cingulate | 1.384 (0.115) | 1.360 (0.117) | 1.650 (0.137) | t=0.656 p=0.516 |
| Substantia Nigra | 2.416 (0.360) | 2.401 (0.346) | 1.614 (0.173) | t=0.138 p=0.891 |
| Dorsal Raphe | 2.970 (0.342) | 2.912 (0.390) | 1.700 (0.139) | t=0.509 p=0.614 |
| Raphe Pontis | 2.566 (0.297) | 2.241 (0.300) | 1.556 (0.253) | t=3.464 p=0.001 |

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|---|---|---|---|---|
| Medulla | 1.571 ( 0.168) | 1.364 (0.210) | 1.464 (0.189) | t=3.501 p=0.001 |

MDS-UPDRS: Movement Disorders Society revised Unified Parkinson's disease Rating Scale
Values expressed as mean (SD); absolute values of t-test/chi-square are presented.

Supplementary Table 1: Bivariate Pearson's correlations (r and p-value) between regional DASB distribution volume ratio and clinical scales in subjects with Parkinson disease.

| | MDS-UPDRS Motor exam [n=23] | Montreal Cognitive Assessment [n=23] | Geriatric Depression Scale [n=23] | Epworth Sleepiness Scale [n=23] |
|---|---|---|---|---|
| Total Cortex | r=-0.137, p=0.533 | r=-0.089, p=0.686 | r=-0.218, p=0.318 | r=0.138, p=0.530 |
| Caudate & Putamen | r=-0.424, p=0.044 | r=0.086, p=0.697 | r=-0.069, p=0.753 | r=0.271, p=0.210 |
| Thalamus | r=-0.250, p=0.251 | r=-0.034, p=0.879 | r=-0.100, p=0.650 | r=0.354 p=0.097 |
| Limbic Cortex | r=-0.137, p=0.533 | r=0.013, p=0.953 | r=-0.221, p=0.310 | r=0.163 p=0.456 |
| Ventral Striatum | r=-0.236 p=0.279 | r=0.149 p=0.499 | r=-0.048 p=0.828 | r=0.382 p=0.073 |
| Ventral Anterior Cingulate | r=-0.234, p=0.282 | r=0.050, p=0.822 | r=-0.261, p=0.229 | r=0.140, p=0.524 |
| Substantia Nigra | r=-0.300, p=0.165 | r= 0.094, p=0.670 | r=0.121, p=0.583 | r=0.586, p=0.003 |
| Dorsal Raphe | r=-0.261, p=0.229 | r=-0.041, p=0.854 | r=0.125, p=0.570 | r=0.452, p=0.030 |
| Raphe Pontis | r=-0.229, p=0.292 | r=0.120, p=0.586 | r= 0.011, p=0.962 | r=0.338, p=0.115 |
| Medulla | r=-0.097, p=0.660 | r=0.041, p=0.854 | r=-0.296, p=0.170 | r=0.287, p=0.184 |

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Supplementary Table 2: Bivariate Pearson's correlations (r and p-value) between regional DASB distribution volume ratio and clinical scales in subjects with Multiple System Atrophy

| | MDS-UPDRS Motor exam [n=14] | Montreal Cognitive Assessment [n=15] | Geriatric Depression Scale [n=14] | Epworth Sleepiness Scale [ n=14] |
|---|---|---|---|---|
| Total Cortex | r=-0.670, p=0.009 | r= 0.196, p=0.485 | r=-0.450, p=0.111 | r=-0.269, p=0.353 |
| Caudate & Putamen | r=-0.682, p=0.007 | r=0.213, p=0.445 | r=-0.429, p=0.126 | r=-0.124, p=0.673 |
| Thalamus | r=-0.527, p=0.053 | r=0.056, p=0.842 | r=-0.177, p=0.546 | r=-0.083, p=0.777 |
| Limbic Cortex | r=-0.593 p=0.026 | r=0.063 p=0.823 | r=-0.450 p=0.107 | r=-0.190 p=0.515 |
| Ventral Striatum | r=-0.774 p=0.001 | r=0.199 p=0.476 | r=-0.383 p=0.177 | r=-0.265 p=0.359 |
| Ventral Anterior Cingulate | r=-0.789 p=0.001 | r= 0.376 p=0.167 | r=-0.408 p=0.147 | r=-0.342 p=0.232 |
| Substantia Nigra | r=-0.484 p=0.080 | r=-0.029 p=0.919 | r=-0.356 p= 0.211 | r=-0.508 p=0.064 |
| Dorsal Raphe | r=-0.380 p=0.180 | r=-0.066 p=0.814 | r=-0.498 p=0.070 | r=-0.033 p=0.912 |
| Raphe Pontis | r=-0.564 p=0.036 | r=0.007 p=0.979 | r=-0.537 p= 0.048 | r=-0.364 p=0.200 |
| Medulla | r=-0.524 p= 0.055 | r=0.180 p=0.522 | r=-0.318 p=0.269 | r=-0.534 p=0.049 |

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Supplementary Table 3: Comparison of Regional DASB DVR between Normal Controls vs. Parkinson disease and Normal Controls vs. Multiple System Atrophy

| Region of Interest | Parkinson disease (PD; n=23) | Multiple System Atrophy (MSA; n=18) | Normal Controls (NC; n=16) | NC vs. PD (t-test, p-value) | NC vs. MSA (t-test, p-value) |
|---|---|---|---|---|---|
| Total Cortex | 1.267 (0.130) | 1.232 (0.093) | 1.792 (0.136) | t=12.205, p <0.001 | t=14.148, p <0.001 |
| Caudate & Putamen | 2.232 (0.182) | 2.210 (0.192) | 2.007 (0.175) | t=3.858, p<0.001 | t=3.201, p=0.003 |
| Thalamus | 2.381 (0.209) | 2.187 (0.164) | 2.103 (0.236) | t=3.887, p<0.001 | t=1.213, p=0.234 |
| Limbic Cortex | 1.553 (0.130) | 1.454 (0.138) | 1.799 (0.144) | t=5.571, p<0.001 | t=7.135, p<0.001 |
| Ventral Striatum | 2.388 (0.194) | 2.205 (0.241) | 1.959 (0.178) | t=7.016, p<0.001 | t=3.349, p=0.002 |
| Ventral Anterior Cingulate | 1.384 (0.115) | 1.360 (0.117) | 1.650 (0.137) | t=6.583, p<0.001 | t=6.664, p<0.001 |
| Substantia Nigra | 2.416 (0.360) | 2.401 (0.346) | 1.614 (0.173) | t=8.249, p<0.001 | t=8.224, p<0.001 |
| Dorsal Raphe | 2.970 (0.342) | 2.912 (0.390) | 1.700 (0.139) | t=14.035, p<0.001 | t=11.758, p<0.001 |
| Raphe Pontis | 2.566 (0.297) | 2.241 (0.300) | 1.556 (0.253) | t=11.089, p<0.001 | t=7.157, p<0.001 |
| Medulla | 1.571 ( 0.168) | 1.364 (0.210) | 1.464 (0.189) | t=1.859, p=0.071 | t=1.443, p=0.159 |

*NC = Normal Control; MSA = Multiple System Atrophy; PD = Parkinson disease; absolute values of t-test/chi-square are presented.

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Supplementary Figure 1
Scatter plots depicting the inverse relationship in MSA subjects (n=14) between MDS-UPDRS motor score and regional DASB distribution volume ratio (DVR) in the A) Total Cortex [top left] B) Caudate & Putamen [top right] C) Ventral Anterior Cingulate [bottom left] and D) Raphe Pontis [bottom right]

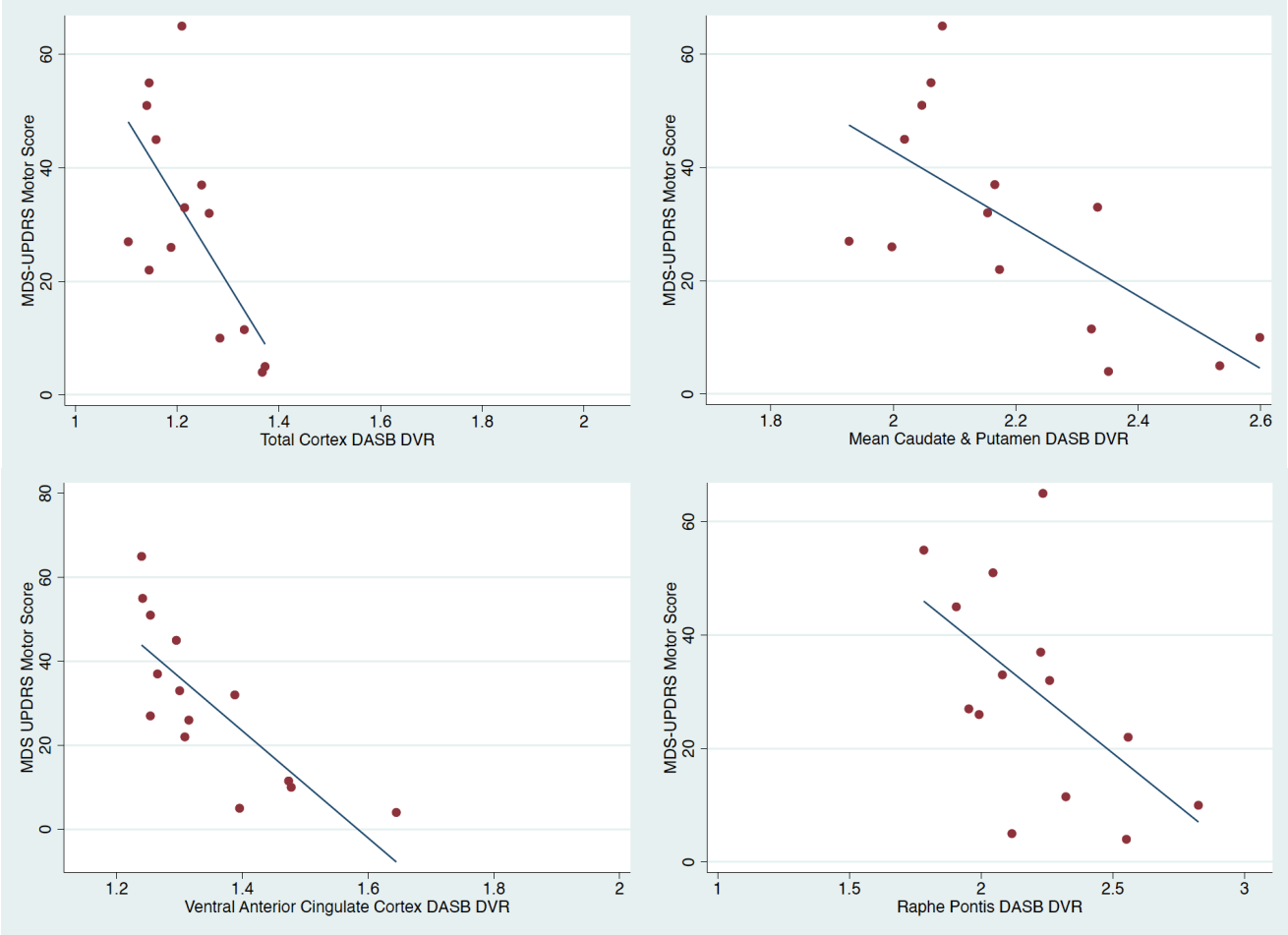

**Figure 1**

Axial images presenting group averages for [$^{11}$C]DASB PET in MSA and PD subjects. White arrows in top rows show reduced [$^{11}$C]DASB binding in MSA compared to PD in several regions of interest.

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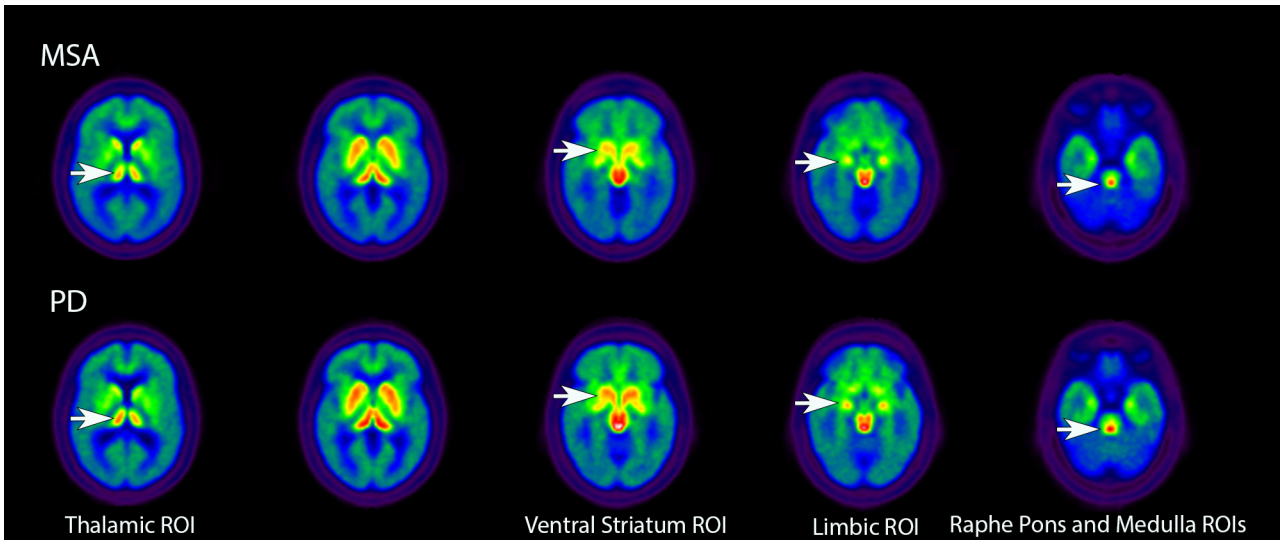


MDS_29220_DASB_DVR_MSA_vs_PD_081022.tif